Water and solute transport across the peritoneal membrane

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Abstract: PURPOSE OF REVIEW: We review the molecular mechanisms of peritoneal transport and discuss how a better understanding of these mechanisms is relevant for dialysis therapy. RECENT FINDINGS: Peritoneal dialysis involves diffusion and osmosis through the highly vascularized peritoneal membrane. Computer simulations, expression studies and functional analyses in Aqp1 knockout mice demonstrated the critical role of the water channel aquaporin-1 (AQP1) in water removal during peritoneal dialysis. Pharmacologic regulation of AQP1, either through increased expression or gating, is associated with increased water transport in rodent models of peritoneal dialysis. Water transport is impaired during acute peritonitis, despite unchanged expression of AQP1, resulting from the increased microvascular area that dissipates the osmotic gradient across the membrane. In long-term peritoneal dialysis patients, the fibrotic interstitium also impairs water transport, resulting in ultrafiltration failure. Recent data suggest that stroke and drug intoxications might benefit from peritoneal dialysis and could represent novel applications of peritoneal transport in the future. SUMMARY: A better understanding of the regulation of osmotic water transport across the peritoneum offers novel insights into the role of water channels in microvascular endothelia, the functional importance of structural changes in the peritoneal interstitium and the transport of water and solutes across biological membranes in general.

DOI: https://doi.org/10.1097/MNH.0000000000000151

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Keywords
aquaporin-1, osmosis, peritoneal dialysis, ultrafiltration

INTRODUCTION

Adequate transport of water and small solutes is key to successful peritoneal dialysis, a renal replacement technique used by more than 200 000 patients with end-stage renal disease worldwide [1]. As compared with haemodialysis, peritoneal dialysis offers increased flexibility and autonomy to patients, along with similar outcomes [2]. Because of its relative simplicity and lower cost, peritoneal dialysis is rapidly growing in many parts of the world [1]. The principle of peritoneal dialysis is to use the peritoneum as a dialysis membrane to continuously draw waste products and excess fluids from the patient's blood towards the dialysate. Peritoneal dialysis involves diffusive and convective transports, and osmosis through the highly vascularized peritoneal membrane.

The peritoneum is a thin, translucent membrane covering the inner surface of the abdominal wall and the majority of the visceral organs. The peritoneum can be viewed as a semi-permeable, heteroporous membrane containing three major components: a monolayer of mesothelial cells; an interstitial tissue consisting of bundles of collagen in a mucopolysaccharide hydrogel; and a dense network of capillaries [3] (Fig. 1a). The endothelium lining peritoneal capillaries and venules offers the major rate-limiting hindrance for the transport of water and solutes during peritoneal dialysis,

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Curr Opin Nephrol Hypertens 2015, 24:434–443
DOI:10.1097/MNH.0000000000000151

KEY POINTS

- AQP1-mediated osmotic water transport significantly contributes to water removal during peritoneal dialysis. AqF026, the first identified AQP1 pharmacological agonist, increases water removal *in vivo*, through interaction with an intracellular gating domain.
- During acute peritonitis and long-term peritoneal dialysis, an increase in the effective peritoneal surface area, for instance due to local inflammation, leads to faster absorption of glucose, early dissipation of the osmotic gradient and loss of ultrafiltration.
- In long-term peritoneal dialysis patients, the fibrotic interstitium reduces the osmotic conductance of the peritoneal membrane, causing ultrafiltration failure. This transport defect is predictive of encapsulating peritoneal sclerosis.
- In a rat model of stroke, peritoneal dialysis efficiently attenuates the transient increase in blood levels of glutamate, thereby reducing propagation of ischemic brain damage, infarct size and degree of disability.
- Liposome-supported peritoneal dialysis is a promising approach to extract endogenous or exogenous metabolites with a high efficiency, potentially relevant for the treatment of metabolic disturbances and drug intoxications.

restricting solute exchange to less than 0.1% of its total surface area [4▪]. Computer simulations suggested the capillary endothelium to be functionally described by a three-pore model [5] (Fig. 1b). This model postulated the existence of small pores (radius, 40–50 Å), located between endothelial cells, accounting for nearly 99.5% of the total pore area available for solute transport and contributing to half the water removal (or ultrafiltration) through solute-coupled water transport; large pores (radius, 250 Å), responsible for the transcapillary transport of macromolecules such as proteins and immunoglobulins during peritoneal dialysis, representing only 0.01% of the total number of pores; and ultrasmall pores (radius, <3 Å), located in endothelial cells, that would facilitate the transport of water but not that of solutes (free-water transport).

Large epidemiological studies have evidenced that parameters of peritoneal solute and water transport are major determinants of outcome in peritoneal dialysis patients [6–8]. Unravelling the molecular mechanisms involved in these transport processes is thus of utmost importance for patients treated by peritoneal dialysis. The present review summarizes current knowledge in this field of research, focusing on recent insights obtained from experimental models of peritoneal dialysis, and from structural, molecular and functional analysis of the human peritoneal membrane in cohorts of peritoneal dialysis patients.

OSMOTIC WATER TRANSPORT AND ROLE OF AQUAPORINS

From a physiological point of view, the phenomenon of osmosis occurs through a barrier restricting the transport of solute compared with that of water. For the peritoneal membrane, the existence of solute-impermeable, ultrasmall pores in the capillary endothelium has been postulated to explain the effectiveness of glucose as an osmotic agent despite its small size (3.7 Å) and the phenomenon of sodium sieving. Sodium sieving consists in the rapid fall in dialysate sodium concentration during a dwell with hypertonic glucose, and is predicted to result from free-water transport across ultrasmall pores. These ultrasmall pores were predicted to have a major clinical importance for peritoneal dialysis by mediating half the ultrafiltration during a dwell with hypertonic glucose [5,9].

In the early 1990s, aquaporin-1 (AQP1) was identified as the archetypal member of a family of membrane water channels, conserved in all living organisms including plants [10–12]. The AQPs are organized as homotetramers in plasma membranes, with each monomer containing six tilted, membrane-spanning α-helices surrounding a single central pore. The selectivity of the pore for water (against protons) is ensured by several elements, including a narrow constriction of 2.8 Å [13], a conserved arginine residue lining the pore and providing a fixed positive charge, a transient reorientation of the water dipole resulting from the simultaneous formation of hydrogen bonding with the side chains of two conserved asparagine residues (NPA [Asn-Pro-Ala] motifs) and two partial positive charges at the centre of the channel resulting from two nonmembrane-spanning α helices [12]. AQP1 was initially discovered in red blood cells and in renal proximal tubule cells [10,12,14], and is also constitutively expressed in endothelial cells lining peritoneal capillaries [14–16] (Fig. 2a,b).

Several lines of evidence demonstrated that AQP1 constitutes the molecular counterpart of the ultrasmall pore in the peritoneal membrane [4▪]. Functional studies conducted in rats and rabbits have shown that classical AQP antagonists such as mercurial agents inhibit water transport across the peritoneum [18,19]. The deletion of *Aqp1* in mice provided critical insights into the role of AQP1 in water homeostasis. The *Aqp1*-knockout mice show a severe defect in their urinary-concentrating ability during water deprivation test (due to a defect in

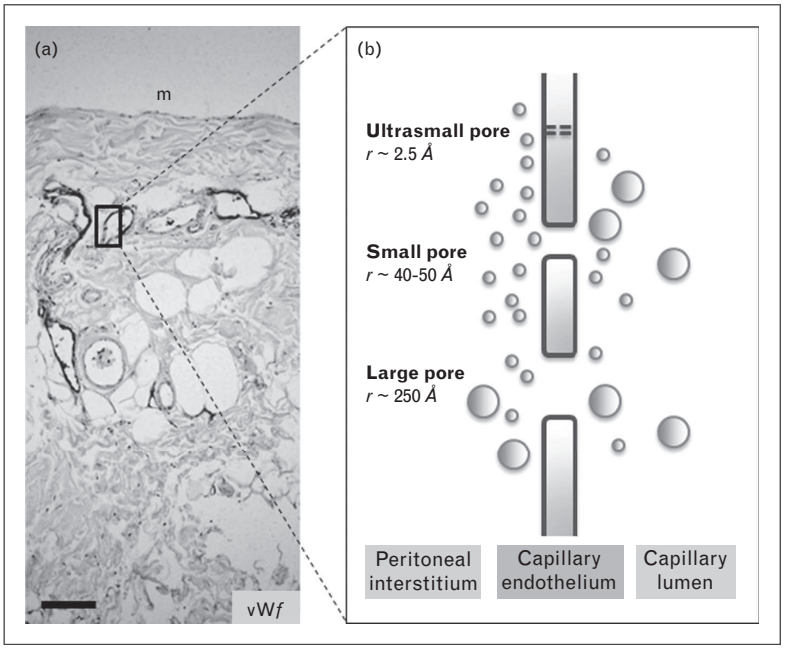

FIGURE 1. Structure of the peritoneal membrane and the three-pore model. (a) Cross-section of the human parietal peritoneum stained for the von Willebrand factor (vWf). m, mesothelium; bar, 100 μm. (b) The three-pore model for peritoneal transport. Å, angström (10^{-10} m); *r*, functional radius. Adapted with permission from [4▪].

creating a hypertonic medullary interstitium by countercurrent multiplication) [20], and a reduced osmotic water transport across the peritoneal membrane [21]. The development of mouse models of peritoneal dialysis [22] as well as novel strategies to accurately assess osmotic water transport *in vivo* [23▪] contributed to delineate the role of AQP1 water channels during peritoneal dialysis. In these models, the deletion of *Aqp1* resulted in a nearly 70% decrease in the initial, solute-free ultrafiltration rate, a nearly 50% decrease in cumulative ultrafiltration, and a complete abolition of the sodium sieving, as compared with their wild-type littermates [17,23▪] (Fig. 2c,d). Taken together, these studies in *Aqp1* mice validated two major predictions of the three-pore model: ultrasmall pores mediate 50% of ultrafiltration during peritoneal dialysis with a hypertonic glucose dialysate; and free-water transport accounts for the observed sodium sieving [4▪,5]. To date, AQP1 is the only identified molecular counterpart that is directly involved in transport processes sustaining peritoneal dialysis.

PERITONEAL SOLUTE TRANSPORT: IMPACT OF LOCAL INTRAPERITONEAL INFLAMMATION

Peritoneal transport of low molecular weight solutes (such as urea and creatinine) occurs by diffusion and convection through small pores, at the level of inter-endothelial clefts, while transport of macromolecules is predicted to occur across large pores [3,24]. The identity of these large pores has not been established, even if some structures have been postulated, including plasmalemma vesicles, vesicular-vacuolar organelles, large interendothelial clefts or venular interendothelial gaps [3].

According to Fick's principles, peritoneal solute transport rate (PSTR) is primarily determined by the number of perfused peritoneal capillaries in contact with the dialysis solution (the effective peritoneal surface area, EPSA), the intrinsic permeability of the membrane and the concentration gradient between blood and dialysate [3]. Data from large cohorts of peritoneal dialysis patients with peritoneal equilibration testing at the initiation of peritoneal dialysis indicate an important – more than two-fold – inter-individual variability in the initial PSTR [25]. This variability is clinically relevant, as faster solute transport is associated with lower peritoneal ultrafiltration capacity (due to early dissipation of the osmotic gradient), and PSTR determines the peritoneal dialysis prescription (dialysate dwell time, dextrose concentration, osmotic agent). Furthermore, higher PSTR has been associated with a greater risk of technique failure, and with an excessive risk of death among patients on continuous ambulatory peritoneal dialysis [7].

The effect of clinical variables (age, ethnicity, comorbidity, level of serum albumin) on initial PSTR

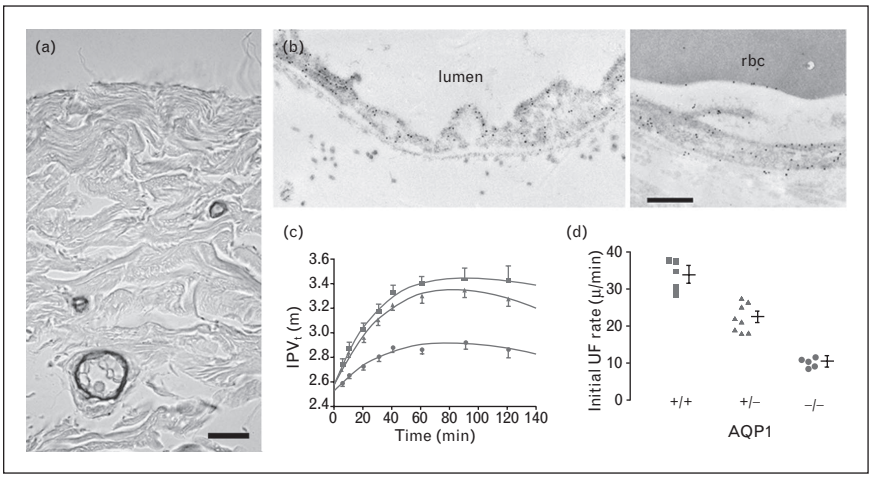

FIGURE 2. Distribution and role of AQP1 in the peritoneal membrane. (a) Cross-section of the human parietal peritoneum stained for AQP1. m, mesothelium; bar, 20 µm. (b) Immunogold labelling of AQP1 on mouse visceral peritoneum. rbc, red blood cells; bar, 500 nm. (c and d) Effect of *Aqp1* deletion on the transport of water across the peritoneal membrane. The intraperitoneal volume versus time curves (IPV_t) (c) and the initial ultrafiltration (UF) rates (d) are determined in $Aqp1^{+/+}$ mice (red symbols), $Aqp1^{+/-}$ mice (blue symbols) and $Aqp1^{-/-}$ mice (green symbols) during a 2-h exchange with hypertonic dialysate. Adapted with permission from [4▪,17].

is only about 30%, suggesting that additional factors account for the inter-individual variability in PSTR [26,27]. Interleukin (IL)-6, a cytokine mediating the acute-phase inflammatory reaction able to increase vascular permeability *in vitro*, is produced by mesothelial and resident cells in the peritoneal membrane [28,29]. Concentrations of IL-6 in the dialysate - taken as a surrogate for intraperitoneal inflammation - have been associated with PSTR [29,30]. The Global Fluid Study, a multinational, multicentre, prospective cohort, including almost 1000 peritoneal dialysis patients, recently confirmed this association, by showing that dialysate IL-6 level is the most important and independent determinant of PSTR in both incident and prevalent peritoneal dialysis patients [31]. Importantly, local intraperitoneal inflammation does not affect patient survival, whereas systemic inflammation – which is associated with advanced age and comorbidity – has been shown to be an independent predictor of death among patients on peritoneal dialysis [31]. Altogether, these data point towards local intraperitoneal inflammation as the most important determinant of EPSA and solute transport in peritoneal dialysis patients; as a result, patients with an inflamed peritoneal membrane are expected to have an enlarged EPSA, high PSTR and increased protein loss in the peritoneal effluent during peritoneal dialysis.

CHANGES IN PERITONEAL TRANSPORT DURING ACUTE PERITONITIS

Acute peritonitis represents a severe complication of peritoneal dialysis and is characterized by recruitment and activation of leukocytes in the peritoneal cavity, higher PSTR and protein loss in the peritoneal effluent, leading to increased absorption of glucose, impaired ultrafiltration capacity and fluid overload [15,32]. Vasoactive substances linked to local inflammation, particularly nitric oxide, contribute to these changes. Inhibition of nitric oxide synthase (NOS) with NG-nitro-L-arginine methyl ester was shown to improve ultrafiltration and to reverse changes in PSTR in rat and mouse models of acute peritonitis [33,34]. The use of acute peritonitis models in mice lacking specific NOS isoforms – neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS) – demonstrated the importance of nitric oxide for structural and transport-related alterations induced by acute peritoneal infection or inflammation. The deletion of eNOS, which had no effect on peritoneal structure or transport at baseline, significantly attenuated the vascular proliferation and the inflammatory infiltrate in a catheter-induced model of Gram-positive bacterial peritonitis, resulting in improved ultrafiltration [35]. Further investigations using a model of lipopolysaccharide-induced peritonitis in mice deficient for each NOS isoform confirmed the specific role of eNOS in mediating increased solute transport and loss of ultrafiltration associated with peritonitis, whereas nNOS and iNOS have no effect [36]. In summary, upregulation of eNOS and local nitric oxide production increase vascular permeability and promote angiogenesis and leukocyte adhesion, thereby contributing to the functional changes in peritoneal transport during acute peritonitis.

CHANGES IN PERITONEAL TRANSPORT DURING LONG-TERM PERITONEAL DIALYSIS

Prolonged exposure to nonphysiologic (acidic, hyperosmolar, with high levels of glucose degradation products) peritoneal dialysis solutions – sometimes with repetitive episodes of peritonitis – causes inflammation and damage to the peritoneal membrane, which undergoes fibrosis, angiogenesis and hyalinizing vasculopathy [37–40]. These morphologic alterations have been associated with increased PSTR and ultrafiltration failure [37–41], thereby constituting an obstacle to long-term peritoneal dialysis, through an increased risk of technical failure, morbidity and mortality (for review, see [39]).

Alternative models have been developed to integrate the structural changes to predict peritoneal transport modifications during long-term peritoneal dialysis. The distributed model was developed from a two-dimensional simulation that integrates the microvasculature with the surrounding cells and interstitium within the peritoneal membrane [42]. This model is particularly appropriate to analyse the influence of parameters such as the local density of blood vessels or the interstitium on the single endothelial permeability [43]. A modified version of the three-pore model included the capillary wall and a serial barrier consisting of fibres in the interstitium to predict more accurately long-term changes in peritoneal transport related to alterations in the microvasculature and interstitial compartment [44].

Predictions from the distributed and serial fibre matrix/pore models were recently verified in a cohort of long-term patients with severe peritoneal remodelling, a feature of encapsulating peritoneal sclerosis (EPS) [45▪]. EPS constitutes the most severe complication of peritoneal dialysis in which an exaggerated fibrogenic response of the peritoneal membrane (Fig. 3) leads to bowel encapsulation and intestinal occlusion (for review, see [46]). Patients who subsequently developed EPS showed an early loss of ultrafiltration capacity and osmotic conductance to glucose [45▪,47,48], and this transport defect was shown to be an independent and powerful predictor of the risk of EPS [45▪]. Recent data indicate that reduced net ultrafiltration and sodium sieving are directly related to the degree of peritoneal fibrosis, and to collagen density and the amount of thick collagen fibres in the submesothelial area, supporting the hypothesis that the fibrotic interstitium restricts water transport *in vivo* [45▪] (Fig. 3). Importantly, the low osmotic conductance and abolition of sodium sieving were not associated with any change in AQP1 expression or density in the peritoneal capillaries of these patients [45▪]. Accumulation of collagen fibres in the interstitium – which normally constitutes a porous matrix across which interstitial fluid flows – has been suggested to decrease hydraulic conductance by at least three mechanisms: exclusion of glycosaminoglycans from the intrafibrillar space, thereby increasing their extrafibrillar concentration; reduction of the mean hydraulic radius in the interstitium, leading to a reduced area for flow; and tortuosity, which increases the path length for flow [49]. These data are in line with predictions from the serial pore-membrane/fibre matrix and distributed models that postulated that severe peritoneal fibrosis reduces osmotic conductance, either through the development of a second – mechanical – barrier outside the capillaries that restricts water transport [44], or by reducing the penetration of the osmotic agent in the peritoneal membrane, thereby limiting the osmotic gradient across the capillary wall [42,43]. Altogether, these data demonstrated that the development of a fibrotic interstitium alters osmotic water transport and provided a direct link between severe peritoneal damage and altered functional characteristics of the membrane.

TARGETED APPROACHES TO MODULATE PERITONEAL TRANSPORT

Prevention and treatment of long-term peritoneal dialysis-associated structural and functional changes in the peritoneal membrane primarily rely on the avoidance of peritoneal aggressions such as peritonitis and chronic exposure to nonphysiological peritoneal dialysis solutions. Interestingly, a recent randomized controlled trial suggested that the use of newer biocompatible peritoneal dialysis solutions (reviewed in [50]) with neutral pH and low levels of glucose degradation products could prevent the increase in small solute transport that is associated with conventional peritoneal dialysis solutions, during a 2-year follow-up [51].

More directly, the critical role of AQP1 in osmotic water transport during peritoneal dialysis suggested that water channels could be potential targets to increase ultrafiltration and to restore fluid balance in peritoneal dialysis patients [17]. The proof-of-principle for that concept was provided by a study in a rat model of peritoneal dialysis [52]. In this model, high-dose dexamethasone increased AQP1 expression in peritoneal capillaries – through a glucocorticoid element response in the promoter of the *Aqp1* gene – and enhanced free-water transport and total ultrafiltration. Importantly, changes in water transport occurred without any modification of solute transport nor change in the osmotic gradient. The effect of corticosteroids on AQP1 expression and

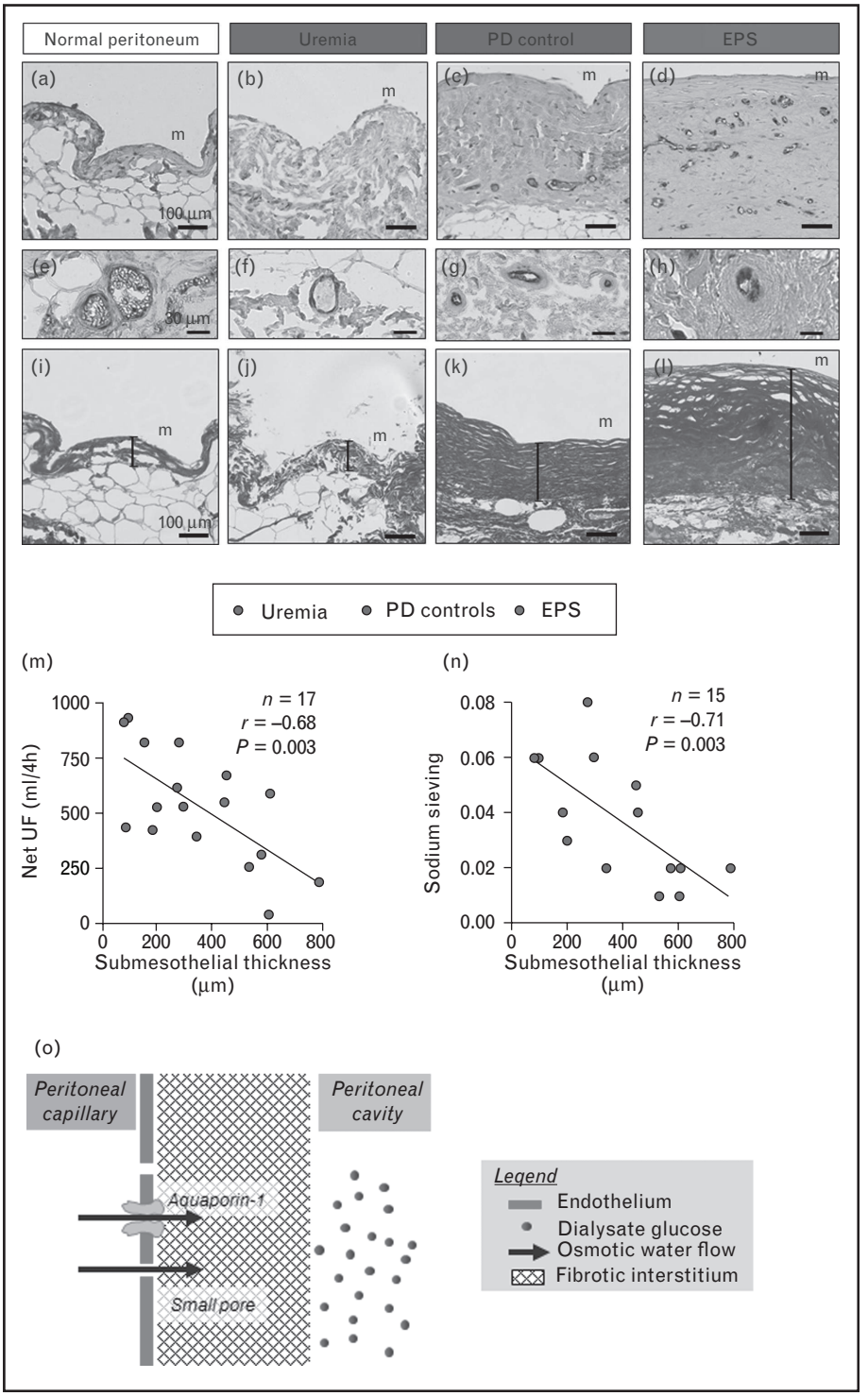

FIGURE 3. Structural changes in the peritoneal interstitium reduce osmotic water transport in patients with encapsulating peritoneal sclerosis (EPS). (a–d) Immunostaining for vWf in normal (a), uremic (b), control peritoneal dialysis (PD) (c) and EPS (d) peritoneum. m, mesothelium; bar, 100 µm. (e–h) Representative sections of peritoneum with evaluation of the degree of vasculopathy in the post-capillary venules stained for vWf in normal (e), uremic (f), control PD (g) and EPS (h) peritoneum. Bar, 30 µm. (i–l) Representative sections of parietal peritoneum from normal (i), uremic (j), control PD (k) and EPS (l) peritoneum stained with picrosirius red. Bar, 100 µm, mesothelium. (m,n) Correlation between net UF (m) or sodium sieving (n), and submesothelial thickness in PD patients. Circles represent individuals; green circles for uremic, blue for PD and red for EPS patients. Peritoneal transport parameters were obtained using a modified 4 h 3.86% glucose-based dialysate PET. (o) The serial three-pore membrane/fiber matrix model, Adapted with permission from [44–45▪].

water transport was recently confirmed in peritoneal dialysis patients, by comparing data from functional testing before and after living-donor kidney transplantation. As compared with results from the pre-transplantation period, peritoneal exchange tests performed in three patients treated with high doses of corticosteroids after kidney transplantation evidenced a two-fold increase in sodium sieving, paralleled by an increase in the ultrasmall pore-water transport, although solute transport and small pore-water transport remained unchanged [53].

In addition to molecules upregulating the expression of water channels, the search for pharmacologic agonists of AQPs emerged as an exciting field of investigation. Initial observations revealed that plants counteract fluctuations in water supply during drought stress or flooding through the gating of their AQPs [54]. X-ray crystallography demonstrated that the rapid gating of plant AQP results from conformational changes of the intra-cytoplasmic loop D, which acts as a cap occluding or opening the internal pore of water channels, in response to de-phosphorylation of conserved serine residues (drought stress), or to protonation of a conserved histidine (flooding) [55]. This gating mechanism appeared conserved throughout all plant plasma membrane AQPs, and recent evidence has suggested it also occurs in mammals. The bumetanide derivative AqB013 (Aq, aquaporin ligand; B, bumetanide scaffold) blocks rat AQP1 and the closely related AQP4 *in vitro*, by a mechanism thought to involve physical occlusion of the intracytoplasmic water channel pore [56]. By screening a large library of arylsulfonamide compounds, AqF026 (Aq, aquaporin ligand; F, furosemide scaffold) was recently identified and characterized as the first known AQP pharmacological agonist [57▪▪] (Fig. 4a). In the *Xenopus laevis* oocyte system, extracellularly applied AqF026 potentiated AQP1 (but not AQP4)-mediated water transport by more than 20%. In-silico docking and site-directed mutagenesis in swelling assays demonstrated the critical role of specific residues located in intra-cytoplasmic loop D, involved in the gating of water channels (Fig. 4b,c). In-vivo experiments using a mouse model of peritoneal dialysis demonstrated that AqF026 enhances AQP1-mediated water transport and total ultrafiltration across the peritoneal membrane (Fig. 4d,f), with no effect on osmotic gradient, solute transport, expression levels of AQP1 and no overt toxicity. The absence of potentiation effects in *Aqp1* knockout mice confirmed that AQP1 is the specific target of AqF026. The development of pharmacological modulators of AQP-mediated water transport such as AqF026, which increases water transport *in vivo*, offers perspectives for peritoneal dialysis and clinical situations associated with disordered fluid balance.

PERITONEAL DIALYSIS FOR NONRENAL INDICATIONS

In addition to its role as renal replacement therapy, an increasing body of evidence suggests that peritoneal dialysis-induced osmosis can help treating fluid overload in patients with refractory heart failure, while improving functional status and quality of life, and reducing morbidity and mortality of these patients [58,59]. Furthermore, the capacity for diffusive transport of glutamate and for trapping toxic molecules into liposomes suggests that peritoneal dialysis may also be useful for the treatment of stroke and drug overdose, respectively.

Ischemic stroke results from a reduction in cerebral blood flow restricted to the territory of a major brain artery. The ischemic peri-infarct zone – which is functionally impaired, still salvageable but at risk for irreversible structural damage – is now considered as a main target for therapy. In this peri-infarct zone, glutamate, the most abundant neurotransmitter in mammals, was shown to play a critical role in the propagation of ischemic brain damage, by a mechanism called excito-toxicity. The local release of glutamate after stroke also enhances brain-to-blood efflux, leading to a transient increase in its blood concentration, a finding that has been associated with disease progression in patients with acute ischemic stroke. In a rat model of stroke, peritoneal dialysis was effective in attenuating the transient increase in blood levels of glutamate after stroke, thereby reducing excito-toxicity and propagation of ischemic brain damage [60▪▪]. This effect was associated with a reduced cerebral infarct size measured 24 h after the arterial occlusion, as compared with rats not treated with peritoneal dialysis. Addition of glutamate to the dialysis solution completely abrogated the reduction in blood glutamate levels and the beneficial effect of peritoneal dialysis on infarct size, demonstrating the critical role of glutamate clearance by diffusion across the peritoneum. These acute benefits were reflected by a significant improvement of tissue viability and functionality, reducing the degree of disability [60▪▪].

The possibility to create nanosized liposomes with a transmembrane pH gradient offers the possibility to trap uncharged molecules (such as ammonia or drug metabolites), which diffuse from the blood into the acidic core of the liposome, become protonated and then retained into the vesicle due to the low diffusion of charged molecules across lipid membranes. Recent data indicate that such liposome-supported peritoneal dialysis (LSPD) is able

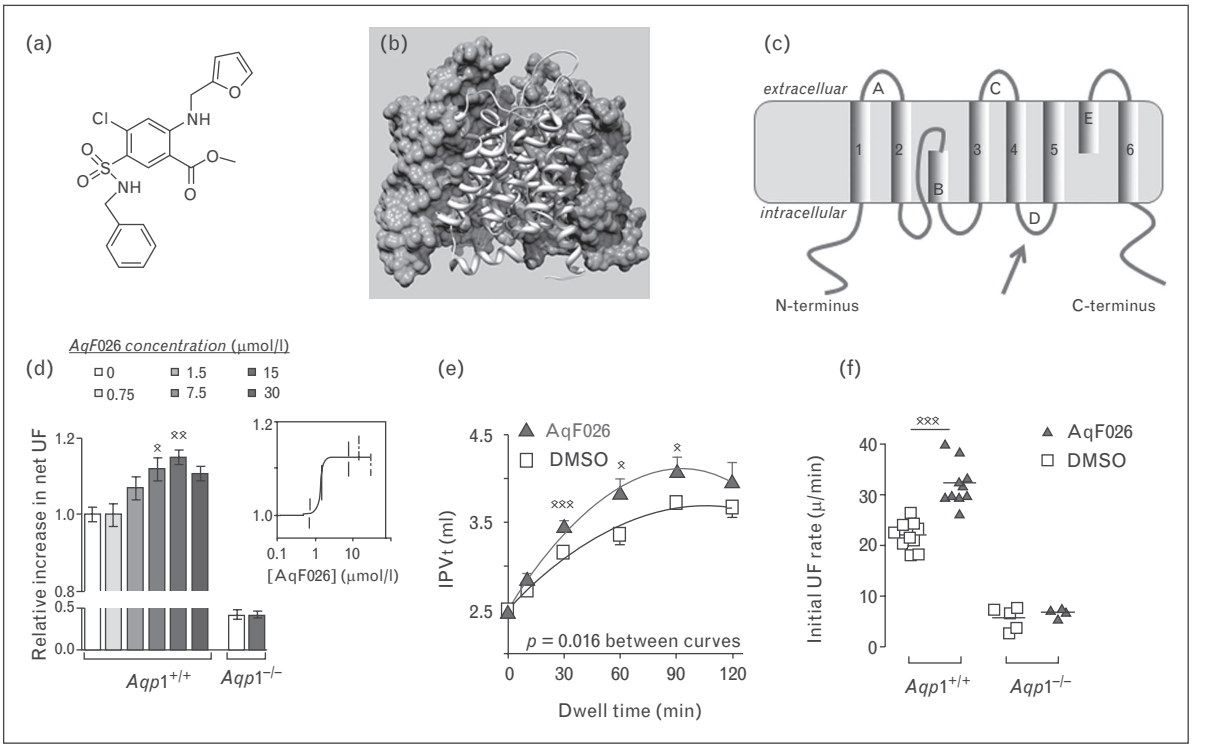

FIGURE 4. AqF026, a novel agonist of AQP1, increases osmotic water transport in vivo. (a) Chemical structure of AqF026. (b) In-silico modelling suggesting a direct interaction of AqF026 at a site located at the intracellular side of AQP1. (c) Intracellular loop D domain (arrow), involved in the gating of AQPs, and critical for the effectiveness of AqF026. (d) Significant, dose-dependent increase in net UF across the peritoneal membrane of wild-type $Aqp1^{+/+}$ mice treated with AqF026. Data are mean±SEM. (e) Increased intraperitoneal volume versus time (IPV_t) among $Aqp1^{+/+}$ mice treated with AqF026 ($P=0.016$ between the AqF026 and vehicle curves). Blue triangles, AqF026-treated animals; open squares, vehicle-treated animals. (f) Increased initial UF rates in $Aqp1^{+/+}$ mice treated with AqF026 ($P<0.001$ versus vehicle). AqF026 has no effect on net UF and initial UF rates in $Aqp1^{-/-}$ mice. DMSO, dimethyl sulfoxide. Data from [57▪▪].

to efficiently extract endogenous ammonia as well as verapamil in rat models [61▪▪]. In-vivo experiments showed that the acidic liposomes (initial internal pH, 3.2) were able to extract endogenous ammonia from the blood in a fast and efficient manner (20-fold enrichment in peritoneal dialysis fluid versus plasma after 3 h of LSPD). LSPD was also tested in a rat model of verapamil intoxication, in which the drug was removed from the circulation much more effectively (30-fold increase) than with peritoneal dialysis alone, resulting in a significant decrease of the deleterious haemodynamic effects of drug poisoning. Apart from verapamil, LSPD was able to extract different basic and acidic drugs often associated with intoxications, including propranolol, amitriptyline, haloperidol, phenobarbital and salbutamol. Furthermore, basic liposomes obtained by using a calcium acetate buffer (internal pH, 10.0) were shown to be able to extract propionic and isovaleric acids *in vitro*, opening perspectives for treatment of congenital metabolic disorders.

The relevance of these animal studies and the possibility to add stroke and endogenous or exogenous intoxications to the list of indications for peritoneal dialysis need now to be rigorously tested in patients.

CONCLUSION AND PERSPECTIVES

The AQP1 water channels play a critical role in water removal during peritoneal dialysis, contributing to the efficiency of the technique, and validating predictions from the three-pore model of the peritoneal membrane. Modulating the expression or activity of AQP1 enhances water transport, opening perspectives to enhance ultrafiltration in peritoneal dialysis patients. The transport of solutes across the peritoneal membrane depends on the EPSA and is influenced by peritoneal inflammation. In peritoneal dialysis patients with acute peritonitis or on long-term peritoneal dialysis, eNOS upregulation or vascular proliferation increases EPSA, contributing to faster solute transport, early dissipation of the osmotic gradient and ultrafiltration failure. Long-term peritoneal dialysis patients who develop an exaggerated peritoneal fibrosis show a reduced

osmotic conductance that is directly associated with quantitative and qualitative changes in the fibrotic interstitium, impeding osmotic water transport. Recent developments suggest that the spectrum of clinical applications of peritoneal transport might extend beyond renal disease and include, in conditions as stroke and intoxications.

Acknowledgements

The authors wish to thank Drs. Eric Goffin and Amadou Sow for fruitful discussions, as well as Yvette Cnops, Huguette Debaix and Sebastien Druart for expert technical assistance.

Financial support and sponsorship

This work was supported by the Fonds National pour la Recherche Scientifique (J.M. and O.D.), the Baxter Extramural Grant Programme (J.M. and O.D.) and the Saint-Luc Foundation (J.M.).

Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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